53. (New) The method of claim 52, wherein the antibody comprises a human constant region.

54. (New) The method of claim 53, wherein the antibody is a chimeric antibody.

55. (New) The method of claim 53, wherein the antibody is a humanized antibody.

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56. (New) The method of claim 53, wherein the antibody is a human antibody.

57. (New) The method of claim 52, further comprising administering CD40 ligand to the subject.

REMARKS

Claims 26-27, 32-33 and 37 were pending in the instant application. Claims 38-57 have been added to more particularly point out and distinctly claim that which Applicants regard as the invention. Support for claims 38-57 can be found in the specification. Support for claims can 38-40 can be found, for example at page 13, line 25, and at page 34, lines 5-6. Support for claims 41, 43, and 50 can be found, *inter alia*, at page 7, lines 24-26 of the specification. Support for claim 42 can be found at page 10, line 3 of the specification. Support for claims 51 and 57 can be found at page 13, lines 27-30. Support for new claims 44-49 and 52-56 can be found at page 24, lines 28-32. No new matter has been added.

After entry of the amendments made herein, claims 26-27, 32-33 and 37-59 will be pending in the present application.

The Rejection Under 35 U.S.C. § 112, First Paragraph, Should be Withdrawn

Claims 26-27, 32-33 and 37 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabling any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. Two grounds for this rejection are presented.

First, the Examiner contends that while the specification is enabling as to "a method for the treatment of mice carrying human transplanted lymphoma and myeloma comprising the administration of a protein which increases the binding of CD40 ligand to the CD40 receptor," the specification "does not reasonably provide enablement for a method of treating humans carrying tumors arising in situ."

Further, the Examiner contends that the claims are overly broad because they cover (1) CD40-expressing cancers of non-B-cell origins and (2) non-CD40 expressing cancers, and such methods allegedly lack predictability.

Applicants respectfully point out that the bases of the Examiner's rejection is alleged lack of utility applied under § 112, since the Examiner questions the predictability of the "use" of the claimed methods and compositions for their intended purposes. Applicants respectfully disagree with the Examiner's rejections for the reasons presented below.

The Legal Standard for Enablement and Utility under 35 U.S.C. § 112, First Paragraph

The Federal Circuit has often set forth the general standard for enablement under 35 U.S.C. § 112, first paragraph. For claims to be enabled, the specification must "teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright*, 27 U.S.P.Q.2d 1510 (Fed. Cir. 1993); *U.S. v. Teletronics Inc.*, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988).

It is clear though that while 35 U.S.C. 112, first paragraph, requires the scope of the claims to be fully enabled, the law does not require the scope of enablement to mirror precisely the scope of the claims. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). To be enabled, all the law requires is that the scope of enablement bear a "reasonable correlation" to the scope of the claims. *Id.* What constitutes "reasonable correlation" in any particular case is a fact sensitive determination, based in part on the state of the art at the time of the invention. *Id.*

The Federal Circuit has addressed whether "reasonable correlation" exists where a specification sets forth certain working examples, specifically murine studies, but the application's claims encompass broader human applications. See *In re Brana,* 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). In that case, applicants appealed a decision by the Patent and Trademark Office rejecting the claims drawn to human treatment as not useful and thus not enabled, in light of a specification disclosing *in vivo* murine studies. The Federal Circuit

reversed the PTO's decision on a finding that data derived from murine studies did not support therapeutic applications in humans. In explaining, the court reiterated its predecessor court's holding that "proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility." 34 U.S.P.Q.2d 1436, 1442 citing *In re Kimmel*, 130 U.S.P.Q. 215, 219 (CCPA 1961).

The Utility Guidelines (M.P.E.P. 706.03(a)(1)) are also applicable when there is an allegation of lack of utility under § 112. As with the case law, under the Utility Guidelines, evidence of utility is sufficient if it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. All that is required is a reasonable correlation between the effectiveness of the methods and the asserted use. (See Utility Guidelines, M.P.E.P. 706.03(a)(1)).

It is important to note that the burden of proving that the enabled examples do not reasonably correlate with the scope of the proposed claims is on the Examiner. A patent applicant's specification which contains a teaching of how to make and use the invention must be taken as enabling unless there is reason to doubt the objective truth of the teachings which must be relied on for enabling support. *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (CCPA 1971). As set forth in the MPEP, "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." MPEP § 2164.02. Furthermore, even if such evidence does exist, "the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition." *Id.* Thus, to support a non-enablement rejection, the Examiner bears the burden of "evaluat[ing] all the facts and evidence and stat[ing] why one would not expect to be able to extrapolate that one example across the entire scope of the claims." *Id.*

The Full Scope of the Present Claims Is Enabled by the Specification

Applicants respectfully submit that the standard of reasonable correlation has been met in this case and consequently, that the full scope of the present claims is enabled by the specification. In support of this contention, Applicants direct the Examiner's attention to the references attached herein and the arguments presented below.

I. *Human Tumors Arising In Situ*

As discussed above, the Examiner states that the data provided in the specification, which demonstrates the anti-tumor activity of the CD40 antibodies of the invention in human tumor cell implant experiments in mice are not enabled for human tumors arising *in situ* (1) because the host-tumor immunorelationship differs between mice and humans, (2) because immune responses to a given antigen differ among species, and (3) because the implanted tumor cells are homogenous in origin whereas tumors arising *in situ* are often heterogenous in nature. Further, the Examiner states that (4) "an effective immunotherapeutic agent must selectively kill tumor cells, not induce an anergy to tumor antigens," and alleges that such selective killing effect has not been demonstrated for the antibodies of the invention.

The Examiner's attention is again directed to the opinion of the Court of Appeals for the Federal Circuit (Federal Circuit) in *In re Brana*, 34 U.S.P.Q.2d 1437 (Fed. Cir. 1995). In *Brana*, the Board had affirmed a final rejection under Section 112, first paragraph, of claims covering certain compounds asserted to be useful as anti-tumor substances because it was alleged that the specification was non-enabling since it did not sufficiently establish that the claimed compounds had a practical utility, *i.e.*, as anti-tumor agents. 34 U.S.P.Q.2d at 1439. In *In re Brana*, mice were injected with specific leukemia cell lines for use as test subjects to measure the antitumor properties of the claimed compounds, in an analogous manner to the experiments presented in Section 8 of the present specification in which myeloma and lymphoma cell lines were administered to experimental mice to demonstrate the anti-tumor effects of administering the anti-CD40 antibodies of the invention. According to *Brana* at 1437, test results showing antitumor activity of compounds against a standard tumor model *in vivo* are acceptable as evidence of utility sufficient to meet the requirement of 35 U.S.C. § 112, first paragraph.

The Examiner has provided several references from which it can be concluded that the anti-tumor effects of a molecule on experimental mice having been injected with a homogenous human cancer cell line will not necessarily be mirrored in human with tumors arising *in situ*. Although Applicants recognize that there may be differences between the responses to the anti-CD40 antibodies of the invention between the mouse model systems employed in the present studies and human tumors arising *in situ*, Applicants respectfully

assert that the stated differences are inconsequential when applying the case law regarding the utility arm of enablement.

It is clear from the discussions of the applicable case law presented herein that the Examiner is applying an inappropriately high standard for establishing utility/enablement. The applicable standard for establishing utility under 35 U.S.C. § 112, first paragraph, is whether there exists a reasonable correlation between the claimed methods and the data put forth by Applicants. In contrast, the Examiner appears to require a perfect correlation between the claimed methods and the data in support thereof. The burden the Examiner is attempting to impose on Applicants to establish utility, that is to provide evidence of the effectiveness of the claimed methods in humans having tumors arising *in situ*, cannot be met without successful human clinical trials. However, as discussed above, the burden of establishing utility under 35 U.S.C. § 112, first paragraph, is met when a compound is effective in a standard animal model. As explained by the Federal Circuit in *In re Brana*:

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.

34 U.S.P.Q.2d at 1442 [emphasis added, quoting *In re Krimmel*, 292 F.2d 948, 953 (CCPA 1961)]. In *Brana*, the Federal Circuit further reminded the Commissioner that testing for the full effectiveness of a product in humans is more properly left to the Food and Drug Administration and the requirements under the law for obtaining a patent should not be confused with the requirements for obtaining government approval to market a particular drug for consumption. *Id.*; *see*, *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994).

Accordingly, based on the foregoing, the standard for establishing utility under 35 U.S.C. § 112, first paragraph, is a reasonable correlation between the results of the experiments described in the instant specification and the claimed methods. Applicants tested the anti-CD40 antibodies of the invention against implants of a human non-Hodgkin's lymphoma cell line (Ramos) and two different human multiple myeloma cell lines (HS Sultan and IM-9) in experimental mice (see Section 8 of the specification, at page 56). These *in vivo* experiments demonstrated that administration of the antibodies of the invention results in tumor-inhibitory effects and increases animal survival. The types of murine studies set forth in the specification are regarded by those of skill in the art as standard experimental

animal models of human cancer. The Examiner's attention is directed to references CF-CH (Ghetie *et al.*, 1990, Int. J. Canc. 45:481-485; Kawata *et al.*, 1994, Cancer Res. 54:2688-94; Cattan and Douglas, 1994, Leukemia Res. 18(7):513-522) of the Supplemental Information Disclosure Statement, all of which establish the well accepted use of tumors arising from implantation of human cancer cell lines in immunocompromised mouse model systems as systems for evaluating the efficacy of human anti-cancer agents. The use of such experimental animals has been validated in the clinical setting. As support for the foregoing, Applicants respectfully direct the Examiner's attention to two references relating to the preclinical evaluation of BEXXAR, an ^{131}I-labeled form of a monoclonal anti-CD20 antibody. In preclinical trials, testing both radiolabeled and unlabeled forms of the anti-CD20 antibody (referred to as "anti-B1") against Raji and Burkitt's lymphomas established in the experimental mice (see Buschbaum *et al.*, 1992, Cancer Research 52:6476-6481; reference CI of the Supplemental Information Disclosure Statement) demonstrated a tumor-inhibitory effects of the antibody. The effectiveness of the mouse experiments has led to successful clinical trials of BEXXAR (See Kaminsky *et al.*, 2001, J. Clin. Oncol. 19(19):3918-28; reference CJ of the Supplemental Information Disclosure Statement).

Based on the data on three cell lines that are accepted in the art as models of human cancers, Applicants submit that one of skill in the art would expect the administration of the anti-CD40 molecules of the invention to have a growth inhibitory effect on human tumors arising *in situ*. Accordingly, in view of the foregoing and of the Federal Circuit's stance on the use of animal models and cancer cell lines in establishing utility and enablement for treatment of cancer claims, Applicants submit the rejection of the present claims under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement of treatment of human tumors arising *in situ* is in error and should be withdrawn.

II. *Non-hematopoietic and non-CD40-expressing Tumors*

As discussed above, the Examiner contends that the claims are overly broad because they cover (1) CD40-expressing cancers of non-B-cell origins and (2) non-CD40 expressing cancers. With respect to CD40-expressing cancers, the Examiner states that "ligation of CD40 in solid tumors does not result in the same surface phenotype as in hematopoietic cells," and thus administration of the anti-CD40 antibodies of the invention may not result in the same growth-inhibiting outcome in such cells. With respect to the

alleged lack of enablement of non-CD40-expressing cancers, the Examiner states that no evidence is provided that suggests that "cross-linking of the putative CD40 receptor on endothelial cells adjacent to a malignant tumor would result in the diminution of said tumor." Applicants submit that for the reasons discussed below, these grounds for rejection are in error and therefore, these rejections must be withdrawn.

A. *Non-Hematological, CD40-Expressing Tumors*

The Examiner alleges that the claims are not fully enabled because, *inter alia*, they encompass treatment of non-hematological, CD40-expressing cancers. The Examiner alleges that because ligation of CD40 in non-hematopoietic tumors does not necessarily produce the same phenotype as in hematopoietic tumors, a different CD40 signaling mechanism exists in these cells and therefore, one of skill in the art would not expect a growth inhibitory outcome of the methods of the invention.

Contrary to the Examiner's allegation that the utility of the claimed methods is unpredictable, Applicants submit that the skilled artisan would predict that the methods of the present invention are useful for the treatment of non-hematological CD40-expressing cancers. Applicants respectfully point out that the Examiner is extrapolating about the predicted outcome of the methods of the present invention from experiments demonstrating the differing effects on various cell types of ligating the CD40 receptor by CD40 ligand alone. Applicants further point out that the antibodies of the invention are not mere ligands. Not only do the antibodies enhance the binding of the CD40 ligand to the receptor, but the antibodies are also known to have an independent signaling capability (*see, e.g.*, Paulie *et al.*, 1989, J. Immunol. 142:590-95, reference BV of record), and may also have a role in promoting an immune response against the tumor cells. These functions of the anti-CD40 antibodies of the invention -- increasing the magnitude of the CD40 ligand signal and independent signaling activities, as well as putative immune stimulatory capabilities-- likely result in a growth inhibitory or apoptotic signal in the context of the organism. Thus, the Examiner's assertion as a basis for the scope of enablement rejection that administration of the anti-CD40 molecules of the invention will necessarily mirror the effects of CD40 ligation and therefore induce growth stimulation in non-hematological cancer cells is in error.

In view of the foregoing, Applicants submit that the Examiner has failed to establish that the scope of the claims does not reasonably correlate with the specification and

therefore, the lack of enablement rejection of the methods of the invention insofar as they relate to non-hematological cancers must be withdrawn.

B. *Non-CD40-Expressing Tumors*

The Examiner alleges that the claims are overly broad because they encompass treatment of non-CD40 expressing cancers. Although CD40 is expressed in the endothelial cells of the blood vessels that sustain such tumors, the Examiner states that the claims are not enabled because there is no evidence that "cross-linking of the CD40 receptor on endothelial cells adjacent to a malignant tumor [] would result in the diminution of said tumor."

In the foregoing statement, the Examiner implies that the only successful outcome of tumor therapy is "diminution" of the tumor. Applicants respectfully disagree. As defined in the specification at page 37, lines 30-34, the term "treatment," as recited in the claims, "shall be deemed to include any clinically desirable or beneficial effect on the disease or disorder, including but not limited to alleviation of one or more symptoms, regression, slowing or cessation or progression, *etc.*" Thus, the invention encompasses using the anti-CD40 antibodies of the invention to achieve beneficial effects other than tumor regression, such as inhibiting tumor growth.

With the definition of "treatment" in mind, the Examiner's attention is directed to Ostrowski and Kinsner (Arch Immunol Ther Exp (Warsz) 2001;49(1):27-31; "Ostrowski," reference CK of the Supplemental Information Disclosure Statement), a review of the state of the art regarding inhibition of angiogenesis as a means to tumor therapy. Ostrowski discusses the integral role of neovascularization in tumor growth (see page 27). Neovascularization, which requires endothelial proliferation, results from a shift in the equilibrium between angiogenic and anti-angiogenic factors favoring angiogenesis (see pages 27-28). Approaches being utilized to inhibit angiogenesis and thus inhibit growth of tumors include monoclonal antibody approaches (see page 30). Ostrowski further confirms that inhibition of tumor growth, rather than tumor regression, is a desirable therapeutic target for cancer therapy.

Given the foregoing, one of skill in the art would predict that an antibody therapy that limits endothelial cell proliferation in the blood vessels that nourish a tumor would inhibit tumor growth and provide clinically useful benefits to the cancer patient. Further, given the fact that the antibodies of the invention have a growth inhibitory effect on several cell types, one of skill in the art would predict, contrary to the Examiner's allegations,

that the methods of the present invention would result in a growth inhibitory effect on endothelial cells and, therefore, that the presently claimed methods would result in therapeutic benefits in cancer patients, including, but not limited to, slowing the growth of cancers that do not express CD40. Accordingly, Applicants request that the rejection of the claims under 35 U.S.C. § 112, first paragraph, on the basis that the methods of the invention are not enabled to the extent they read on treatment of non-CD40-expressing tumors be withdrawn.

CONCLUSION

Applicants respectfully request that the above-made amendments and remarks be entered and made of record in the file history of the present application. In view of the remarks above, it is submitted that all the outstanding rejections have been obviated. Further, it is submitted that the claims are in form for allowance. If any issues remain, the Examiner is respectfully requested to telephone the undersigned at (212) 790-2247 to discuss any issues or questions.

Respectfully submitted,

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Enclosures